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ORIGINAL REPORT

Phase II Trial of Bevacizumab in the Treatment of Persistent or Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study

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ABSTRACT

Purpose
Vascular endothelial growth factor is a key promoter of tumor progression in cervical carcinoma. The Gynecologic Oncology Group (GOG) conducted a phase II trial to assess the efficacy and tolerability of bevacizumab, a recombinant humanized anti–vascular endothelial growth factor monoclonal antibody.

Patients and Methods
Eligible patients had recurrent cervical cancer, measurable disease, and GOG performance status ≤ 2. Treatment consisted of bevacizumab 15 mg/kg intravenously every 21 days until disease progression or prohibitive toxicity. Primary end points were progression-free survival (PFS) at 6 months and toxicity.

Results
Forty-six patients were enrolled (median age, 46 years); 38 patients (82.6%) received prior radiation as well as either one (n = 34, 73.9%) or two (n = 12, 26.1%) prior cytotoxic regimens for recurrent disease. Grade 3 or 4 adverse events at least possibly related to bevacizumab included hypertension (n = 7), thrombo-embolism (n = 5), GI (n = 4), anemia (n = 2), other cardiovascular (n = 2), vaginal bleeding (n = 1), neutropenia (n = 1), and fistula (n = 1). One grade 5 infection was observed. Eleven patients (23.9%; two-sided 90% CI, 14% to 37%) survived progression free for at least 6 months, and five patients (10.9%; two-sided 90% CI, 4% to 22%) had partial responses. The median response duration was 6.21 months (range, 2.83 to 8.28 months). The median PFS and overall survival times were 3.40 months (95% CI, 2.53 to 4.53 months) and 7.29 months (95% CI, 6.11 to 10.41 months), respectively. This compared favorably with historical phase II GOG trials in this setting.

Conclusion
Bevacizumab seems to be well tolerated and active in the second- and third-line treatment of patients with recurrent cervical cancer and merits phase III investigation.

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INTRODUCTION

Although likely an underestimate, Parkin et al[1] reported that cervical cancer affected 493,243 women worldwide in 2002, thereby making it the second most common female cancer. In addition, it is the third most common cause of female cancer mortality annually with 273,505 deaths reported. In developed countries such as the United States, cervical cancer incidence and mortality rates have declined approximately 75% over the last three decades. Still, the disease remains a serious American health threat with an estimated incidence and mortality of 11,150 and 3,670 in 2007, respectively.[2]

Cervical cancer is preventable and is usually curable if detected early.[3] Treatment paradigms in the primary management of cervical cancer are well established with early lesions generally being treated surgically and locally advanced lesions being managed with concurrent cisplatin chemotherapy and pelvic radiation.[4,5] Metastatic disease or recurrent lesions not amenable to radical local excision or regional radiation are treated with palliative chemotherapy. The Gynecologic Oncology Group (GOG) has reported on seven randomized phase III trials in this setting, with only one regimen being superior to single-agent cisplatin administered intravenously at 50 mg/m^2 every 3 weeks.[6] This trial showed that adding topotecan 0.75 mg/m^2 on the first 3 days of a 21-day cycle to cisplatin prolonged the median survival time by 2.9 months (from 6.5 to 9.4 months; $P = .017$) with an unadjusted relative risk estimate

for survival of 0.76 (95% CI, 0.593 to 0.979; $P = .017$, one tailed) compared with cisplatin alone.[7] Although the cisplatin-topotecan doublet is associated with more bone marrow suppression compared with cisplatin alone, there was no decrement in quality of life associated with the combination.[8]

Prognostic factors shown to be important in predicting outcome in the treatment of recurrent cervical cancer include the interval from initial therapy to the time of recurrence, number of prior chemotherapy regimens including prior radiotherapy-sensitizing cisplatin, site of recurrence (with lesions in an irradiated field having a lower chance of response), and worse baseline quality of life.[7-10]

The GOG is currently performing its eighth randomized phase III clinical trial (Protocol 204) in recurrent cervical cancer, and this trial is designed to determine the optimal cisplatin doublet. This four-arm study evaluates four cisplatin combinations including topotecan, paclitaxel, vinorelbine, and gemcitabine. This definitive trial will clarify which platinum doublet is optimal in this setting, making further significant advances in cytotoxic therapy in recurrent cervical cancer even more difficult.

Clearly, more effective agents are needed to treat women with advanced and recurrent cervical carcinoma. With angiogenesis being a pivotal pathway in cervical carcinogenesis and progression, targeting this pathway is rational. Several authors have reported a strong association with vascular endothelial growth factor expression in cervical cancer and poor prognosis.[11,12] Bevacizumab is a humanized antivascular growth factor (vascular endothelial growth factor) monoclonal antibody that has shown activity in many solid tumors.[13] Thus, the GOG conducted a phase II trial of single-agent bevacizumab in patients with persistent or recurrent cervical cancer. At the time this study was designed (circa 2001), bevacizumab was not expected to have a significant, cytotoxic effect on existing tumor cells, so the drug was evaluated as a cytostatic agent. For this reason, the primary end points of this study were the proportion of patients with progression-free survival (PFS) for at least 6 months and the frequency and severity of adverse events. The secondary objectives were to estimate the probability of clinical response, the distribution of overall survival (OS), the distribution of PFS, and the impact of potential prognostic factors on PFS or OS.

PATIENTS AND METHODS

Eligibility criteria included patients with persistent or recurrent squamous cell carcinoma of the cervix (including adenosquamous tumors) that was measurable by Response Evaluation Criteria in Solid Tumors;[14] one or two prior cytotoxic regimens, not including prior cisplatin-based chemotherapy concomitantly administered with primary pelvic radiation; GOG performance status (PS) of 0 or 1, with PS level 2 allowed in patients having received only one prior cytotoxic regimen; and adequate hematologic (absolute neutrophil count $\geq$ 1,500/μL and platelets $\geq$ 100,000/μL), renal (serum creatinine $\leq 1.5\times$ the institutional upper limit of normal [ULN]; if higher, then creatinine clearance $>$ 60 mL/min was required), hepatic (serum bilirubin $\leq 1.5\times$ ULN, and both AST and alkaline phosphatase $\leq 2.5\times$ ULN), and coagulation (prothrombin time such that international normalized ratio is $\leq$ 1.5 or between 2.0 and 3.0 for patients on stable doses of therapeutic anticoagulants and partial thromboplastin time $< 1.2\times$ control) laboratory values. Documentation of tumor type was confirmed by central review by the GOG Pathology Committee.

Patients with nonsquamous tumors (eg, adenocarcinomas), other malignancies evident within 5 years, prior noncytotoxic therapy for management of recurrent or persistent cervical cancer, nonhealing wounds, infection requiring antibiotics, active bleeding, coagulopathy, or CNS disease (primary brain tumor history, brain metastases, uncontrolled seizure disorder, or cerebrovascular accident within 6 months) were ineligible. Patients were also excluded for significant cardiovascular disease (uncontrolled hypertension, myocardial infarction or angina within 6 months, New York Heart Association $\geq$ grade 2 congestive heart failure, or cardiac arrhythmia requiring medication), modified Fontaine $\geq$ grade 2 peripheral vascular disease or claudication within 6 months, $\geq$ 1.0 g of proteinuria per 24 hours, pregnancy or nursing, prior therapy with bevacizumab, or major surgical procedures within 28 days or anticipated while on study.[15] The study received local institutional review board approval at participating institutions, and all patients gave informed consent according to institutional and federal guidelines before enrollment.

Enrolled patients were to receive bevacizumab 15 mg/kg intravenously every 21 days with no dose modification except in cases when there was at least a 10% change in body weight. This dose and schedule of bevacizumab were selected because of the average 21-day half-life of the drug when administered systemically, the dose density similar to that used in active phase II trials in other disease sites, and the potential for combining bevacizumab with standard primary cytotoxic therapy regimens in future phase III trials for patients with cervical cancer.[13]

Toxicity was monitored with history, physical examination, and laboratory assessment before each treatment cycle, with adverse events defined and graded according to National Cancer Institute Common Toxicity Criteria version 2.0.[16] Bevacizumab was to be held for grade 3 nonhematologic toxicity for a maximum of 3 weeks to allow resolution to grade 1 or less. Treatment was discontinued for any grade 4 nonhematologic toxicity.

Activity of bevacizumab was assessed according to Response Evaluation Criteria in Solid Tumors either by palpation before each cycle for peripheral lesions or by computed tomography or magnetic resonance imaging at baseline and before every other cycle for the last 29 patients after amending the protocol (the first 17 eligible and assessable patients were evaluated before cycles 5, 7, 9, and so on, skipping the evaluation before cycle 3) for the measurement of target lesions, the classification of clinical response, and the determination of disease progression.[14] Therapy was discontinued for disease progression, unacceptable toxicity, receipt of other anticancer therapy, or voluntary withdrawal.

The level of activity that would be considered interesting for future phase III studies was determined from an evaluation of historical control data involving six GOG trials performed in similar patients to those enrolled onto the current study (Table 1).[17-22] Because cytostatic agents are often better tolerated than cytotoxic agents, the purpose of the protocol was to screen agents for any activity greater than a limit that is considered clinically uninteresting. This limit was established with the help of previously reported studies. The historical phase II trials included the use of some agents such as cisplatin, topotecan, and gemcitabine, which have been studied in GOG phase III trials in recurrent cervical cancer, as well as other agents with minimal to modest activity such as isotretinoin plus interferon alfa, altretamine, and etoposide.[17-22] The latter agents were selected for comparison and used to help establish that 10% PFS at 6 months was uninteresting.

Bevacizumab was to be considered interesting if eight or more patients survived (progression free) for $\geq$ 6 months, assuming an accrual of 46 to 51 patients. Specifically, using a two-stage design, the targeted sample size for the first stage of accrual was 22 eligible and assessable patients but was permitted to range from 19 to 26 patients for administrative reasons. If there were more than two of 19 to 25 patients or more than three of 26 patients alive and progression free for at least 6 months and medical judgment indicated, accrual to the second stage of the trial was to be initiated. Otherwise, the treatment regimen was to be classified as clinically uninteresting without any additional accrual. If the study advanced to the second stage, then an overall sample size of 47 eligible and assessable patients was targeted but was permitted to range from 44 to 51 patients. If there were no more than six of 44 to 45 patients or no more than seven of

Table 1. Historical Database Used to Help Assess the Activity of Bevacizumab in GOG Protocol 227-C Among Women With Recurrent Cervical Cancer After Experiencing Treatment Failure With One or Two Cytotoxic Regimens (not including chemotherapy with primary radiation)

Protocol Study Section	Agents Studied	No. of Eligible and Assessable Patients	Probability of PFS > 6 Months*		Median Survival (months)	Response	
			Estimate	SE		No. of Patients	%
127B[17]	Isotretinoin and interferon alfa	34	0.06	0.04	3.9	1	3
127C[18]	Cisplatin and pentoxifylline	44	0.20	0.06	6.0	4	9
127D[19]	Altretamine	29	0.03	0.03	4.6	0	0
127F[20]	Topotecan	40	0.15	0.06	6.6	5	12
127H[21]	Etoposide	24	0.12	0.07	3.7	2	8
127K[22]	Gemcitabine	25	0.04	0.04	4.8	2	8
227C (current report)	Bevacizumab	46	0.24	0.06	7.3	5	11

NOTE. There are no study sections labeled A, E, G, I, J, or O.
Abbreviations: GOG, Gynecologic Oncology Group; PFS, progression-free survival.
*Product limit estimate of the cumulative probability of surviving progression-free > 6 months.

46 to 51 patients who were alive and progression free after 6 months, then the regimen was to be considered clinically uninteresting. For a true probability of being alive and progression free after 6 months of 25%, the average probability of correctly classifying the treatment as active was 90%; whereas for a true probability of 10%, the average probability of designating the treatment as active (a false-positive misclassification) was 10%, and the average probability of stopping after completing the first stage of accrual was 64%.[23] The distribution of PFS and OS for patients on this study was described using Kaplan-Meier plots and median estimates. Prognostic factors were evaluated with Cox proportional hazards models using end points for PFS and OS. The factors assessed included age (in years), exposure to prior radiation therapy, one versus two prior chemotherapy regimens, African American versus other race, performance status of 0 or worse, and location of target tumor within or outside the zone of prior radiation. We also examined prior cisplatin use as a sensitizer to radiation; because the amount of missing data in this analysis was high (15 observations, corresponding to approximately 33% of the patients), this analysis was conducted separately. All of the analyses, regardless of the level of missing data, were considered exploratory, and given the small sample size and the number of relationships examined, all results were considered hypothesis generating rather than hypothesis testing. The reported *P* values were considered indicators of possible association but were not meant to be interpreted as statistically significant in the traditional sense.

RESULTS

Patient Characteristics

From April 2002 through November 2006, 50 patients were enrolled, of whom four were excluded (one for wrong histologic cell type, one for wrong primary tumor site, one for inappropriate prior therapy, and one for no documentation of treatment). Thus, the study sample consisted of 46 patients with a median age of 46 years (range, 29 to 62 years); 32 patients (69.6%) were white, and 22 patients (47.8%) had a GOG performance status of 0. Disease characteristics of the study group are listed in Table 2.

A total of 254 cycles of bevacizumab were administered, with a median of four cycles per patient. As of April 2008, 44 patients have discontinued therapy, 36 for disease progression, four for toxicity (all as a result of thrombosis), one for bowel obstruction, one for refusal of further therapy, and one for thrombosis not related to treatment. One patient died on treatment of a grade 5 infection possibly attributed to therapy. Thirty-seven patients died of disease progression, and one patient died from disease and treatment (the grade 5 infection noted earlier). Eight patients (17.4%) are alive; three of these patients are alive without progression with two remaining on treatment.

Table 2. Patient and Clinical Characteristics

Characteristic	No. of Patients	%
Age, years		
20-29	1	2.2
30-39	11	23.9
40-49	17	37.0
50-59	12	26.1
60-69	5	10.9
Race/ethnicity		
Asian	3	6.5
African American	4	8.7
Hispanic	6	13.0
American Indian	1	2.2
White	32	69.6
Performance status		
0	22	47.8
1	23	50.0
2	1	2.2
Cell type		
Adenosquamous	3	6.5
Squamous cell carcinoma	43	93.5
Grade		
1 (well differentiated)	3	6.5
2 (moderately differentiated)	25	54.3
3 (poorly differentiated)	18	39.1
Prior chemotherapy*		
1 prior regimen	34	73.9
2 prior regimens	12	26.1
Prior radiation		
No	8	17.4
Yes	38	82.6
Prior hysterectomy		
No	20	43.5
Yes	26	56.5

*Chemotherapy was not administered in conjunction with primary radiation because a radiotherapy sensitizer is not counted under prior chemotherapy.

Adverse Events

As shown in Table 3, safety of bevacizumab in all 46 patients was analyzed descriptively; events listed had been reported as at least possibly related to study drug. There were eight events related to grade 3 hematologic toxicity (no grade 4). Five patients experienced a deep venous thrombosis, one with pulmonary embolus. There were no cases of arterial thrombosis. There was one episode of grade 4 vaginal bleeding and one grade 4 urinary fistula. From the standpoint of other nonhematologic toxicities, bevacizumab was well tolerated in this cohort. Other notable grade 3 and grade 4 events included hypertension (seven grade 3 and zero grade 4 events), other cardiovascular (two grade 3 and zero grade 4 events), GI (three grade 3 events and one grade 4 event), and genitourinary/renal (two grade 3 events and one grade 4 fistula). Finally, there was no grade 4 proteinuria or hypertension requiring discontinuation of therapy, although there was one grade 5 infection as mentioned earlier.

Activity of Bevacizumab

The activity of bevacizumab was analyzed in 46 patients. Eleven patients (23.9%; two-sided 90% CI adjusted for the interim decision rule [Clopper and Pearson[24]], 14.0% to 36.5%) survived progression free for at least 6 months, and five patients (10.9%; two-sided exact binomial 90% CI, 4.4% to 21.5%) experienced partial responses. The median response duration was 6.21 months (range, 2.83 to 8.28 months). The median PFS and OS times for all patients were 3.40 months (95% CI, 2.53 to 4.53 months) and 7.29 months (95% CI, 6.11 to 10.41 months), respectively. The graph of the Kaplan-Meier estimates of PFS and OS for the study population is shown in Figure 1.

Table 3. Adverse Events

Adverse Effect	Grade (No. of patients) 0	1	2	3	4	Total No. of Patients
Leukopenia	39	3	3	1	0	46
Thrombocytopenia	43	3	0	0	0	46
Neutropenia	42	2	1	1	0	46
Anemia	26	8	10	2	0	46
Other hematologic	41	1	0	4	0	46
Allergy	45	1	0	0	0	46
Hypertension	33	4	2	7	0	46
Thrombosis embolism	41	0	0	4	1	46
Other cardiovascular	34	8	2	2	0	46
Coagulation	43	2	0	1	0	46
Constitutional	22	16	6	2	0	46
Dermatologic	36	5	5	0	0	46
GI	25	7	10	3	1	46
Genitourinary/renal	34	6	3	2	1	46
Hemorrhage	38	5	2	0	1	46
Hepatic	35	11	0	0	0	46
Infection*	40	0	3	2	1	46
Metabolic	29	16	0	1	0	46
Neuropathy sensor	41	3	2	0	0	46
Other neurologic	41	2	3	0	0	46
Pain	27	8	5	6	0	46
Pulmonary	38	1	5	2	0	46

NOTE. The maximum severity of each adverse event per patient, graded according to Common Toxicity Criteria version 2.0, is reported. Events were restricted to those reported as at least possibly related to study drug.
*Listed grade 4 infection is actually grade 5.

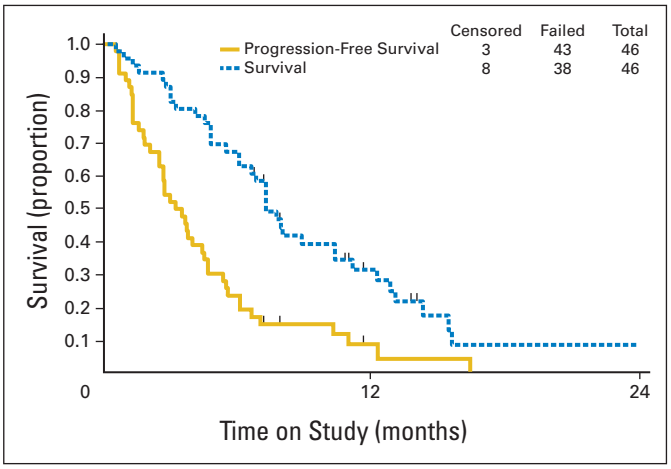

Fig 1. Overall survival and progression-free survival Kaplan-Meier plots for the 46 patients in the study sample.

The PFS in this study is shown with the PFS of studies in the GOG historical database in Figure 2.

Exploratory Analysis of Patient Characteristics and PFS and Survival During Treatment With Bevacizumab

Results of the exploratory analyses are reported in Table 4. Race and performance status may be associated with PFS and OS. African Americans seemed to be younger (mean age of 35 years *v* 48 years for other races), had a worse PS, and had less prior chemotherapy before coming onto this study. This may explain some of the results seen jointly. A separate analysis of the potential effects of prior cisplatin as a radiation sensitizer showed no significant results with regard to PFS or OS.

DISCUSSION

When detected early, cervical cancer is almost always controlled with regional therapy. However, when women with metastatic

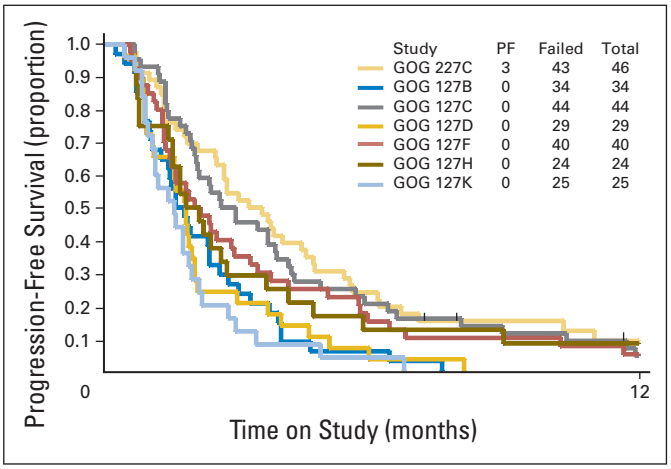

Fig 2. Nonrandomized comparison of progression-free survival (PFS) for studies listed in Table 1 and the PFS from Gynecologic Oncology Group Protocol 227-C (current study) with bevacizumab (light yellow). PF, progression free.

Table 4. Exploratory Analysis of Prognostic Factors

Variables in Model*	Score χ^2	−2LL†	HR Estimate‡	Wald *P*
Progression-free survival				
None	—	256.233	—	—
Race	4.04	253.345	2.83	.054
PS	3.49	252.758	1.84	.065
Age	3.37	252.822	−3.2%	.069
PRCT	0.29	255.938	1.21	.593
PRRT	0.24	256.006	1.23	.626
Age, PS	6.82	249.361	−3.2%, 1.84	.069, .066
Race, PS	6.39	250.913	2.28, 1.70	.137, .121
Race, age	5.68	251.610	2.00, −2.4%	.244, .192
Race, PS, age	8.24	248.901	1.54, 1.75, −2.7%	.485, .102, .160
Overall survival				
None	—	224.054	—	—
PS	5.56	218.591	2.21	.022
Race	3.43	221.532	2.61	.075
PRCT	3.15	221.248	0.52	.081
Age	0.65	223.399	−1.5%	.421
PRRT	0.27	223.797	1.25	.605
PS, race	7.92	217.060	2.07, 2.09	.037, .178
PRCT, PS	7.56	216.845	0.60, 2.06	.174, .038
PRCT, race	7.51	217.656	0.45, 3.33	.040, .031
PRCT, PS, race	10.69	214.436	0.52, 1.88, 2.66	.095, .076, .088

NOTE. Three of the four African Americans had a PS of 1 *v* 0; however, all received only one prior chemotherapy regimen. The mean age of African Americans was 35 years compared with a mean age of 48 years in all other races.

Abbreviations: HR, hazard ratio; PS, performance status; PRCT, prior chemotherapy; PRRT, prior radiation therapy.

*Models that include African American cofactors are indicated by the word race.

†−2 × the logarithm of the likelihood function.[24a]

‡Hazard ratios are for African Americans *v* all other races, for having performance status 1 or 2 *v* 0, for the percent change in hazard for each yearly increase in age, for having one *v* two prior chemotherapy regimens, and for having *v* not having prior radiation.

disease (stage IVB) or recurrent lesions not amenable to salvage surgery or radiation are treated with current systemic cisplatin combination regimens, the median survival is only 9 to 10 months.[4,6,7] To date, no targeted or biologic agents have shown activity in the management of patients with advanced or recurrent cervical carcinoma. Classes of agents with potential activity include epidermal growth factor receptor active agents, therapeutic human papillomavirus vaccines, oncolytic viruses, and antiangiogenesis compounds.

Although angiogenesis is clearly related to cervical cancer development and tumor progression, the tumor shrinkage resulting from cytotoxic therapy (radiation and or chemotherapy) seems to be related to an increase in mature/functional vascularity, thereby improving tumor oxygenation and chemotherapy delivery and facilitating apoptosis. To the contrary, we hypothesize that phenotypically distinct, disorganized, and leaky vascular networks, as measured by CD105 immunostaining, inefficiently deliver oxygen and chemotherapy to the tumor site and may also be markers of poor prognosis for yet unknown reasons.[25] The current study was designed to test the therapeutic benefit of single-agent bevacizumab, an antiangiogenesis compound, and also to prospectively evaluate the role of angiogenesis tissue markers in predicting response; however, difficulty in collecting tumor specimens from recurrent lesions precluded this analysis. Nonetheless, assuming development of more feasible methods, discovery of predictive markers of outcomes to antiangiogenic therapy is an important translational objective in future clinical trials for cervical cancer.

When compared with a database of cytotoxic single-agent compounds studied by the GOG in the setting of treatment failure with one prior regimen for metastatic cervical cancer (Table 1), bevacizumab showed remarkable activity in the present study, with a response rate of 11% and 24% of patients remaining without progression after 6 months on protocol. This level of activity in the current report justifies a phase III trial of bevacizumab in advanced and recurrent cervical cancer.

The present study did not identify any new toxicities or an increased frequency of currently reported toxicities of bevacizumab. Bevacizumab has an extensive safety profile even among patients with prior radiation, as in the current report.[26]

In an attempt to identify factors predictive of outcome after treatment with bevacizumab, in the setting of recurrent cervical cancer, that could be studied prospectively in larger prospective trials, exploratory hypothesis-generating analyses were performed. These analyses suggested an increased risk of progression (or death) for those who are African American, young, and have poor performance status. This is consistent with other GOG cervical cancer trials both in the primary and the recurrent setting.[9,27] The explanation for the prognostic significance of these factors is unclear, and models have been constructed using these parameters from prior phase III GOG trials that predict the likelihood of not responding to existing cytotoxic therapies,[9] making clinical trials investigating novel targeted agents, such as the current study, critical to improving outcomes among these high-risk patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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